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Human maternal-fetal lactate relationships

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1 Introduction

The advent of rapid means for measuring blood lactate levels in capillary blood samples [6, 14] has spurred renewed interest in lactic acidosis and its applicability to the evaluation of fetal stress during labor. Lactic acid constitutes only one of the fixed acids that accumulate during metabolic acidosis [10]. Nevertheless, it is the major specific end-product of anaerobic metabolism, and its accumulation at high concentrations in brain tissue causes edema and necrosis [8]. Moreover, the degree of fetal metabolic acidosis may be better reflected by the blood lactate level than by the base deficit, since the latter is usually not measured directly, but calculated by the blood gas machine from the pH and pCO_2 using a nomogram which is based on adult blood [13]. This tends to overestimate the base deficit in fetal blood, which has a different hemoglobin and different buffering characteristics from adult blood. Actually, the mild metabolic acidosis that is observed in the normal human fetus during labor has been thought to arise in the fetus itself, based on the observation of higher lactate levels in the fetus than in the mother [2, 4, 7, 9], with a net transfer of lactate to the maternal circulation [4]. Other investigators, however, have reported that it is mostly maternal in origin with simple diffusion of lactate across the placenta to the fetus [3, 15]. Thus, the transport and metabolism of lactate by the human feto-placental unit remains ill-defined.

It is the purpose of the present study to examine the metabolic characteristics of the fetoplacental unit as reflected by the blood lactate levels in maternal and umbilical cord blood at the time of delivery in normal and in depressed newborns, and to investigate the way in which the human placenta handles lactate.

2 Material and methods

Umbilical arterial and venous blood samples were obtained immediately after clamping of the cord in 132 liveborn infants. Simultaneous maternal radial arterial samples were also obtained in all cases. The specimens were collected anaerobically into preheparinized polyethylene syringes and analyzed immediately for pH and blood gases using a Corning pH/Blood Gas 165 Analyzer. They were also analyzed for whole blood lactate using the enzymatic-electrochemical method incorporated into the Roche Lactate Analyzer 640, in accordance with the technique outlined by SOUTTER et al. [14]. The performance characteristics of this method are similar to those of the classical but more time-consuming enzymatic-spectrophotometric methods, and it is highly correlated with them [6, 14]. A sample volume of 200 microliters was sufficient to obtain all the measurements, and the results were available within minutes. The base deficit was calculated using the SIGGAARD ANDERSEN nomogram [13].

The newborns were carefully assessed for APGAR scores at 1 and 5 minutes, and were divided into the following four groups:

- Group A, comprising 64 newborns delivered by elective cesarean section before the onset of labor, whose 1-minute APGAR score was 7 or higher. These babies were not subjected to any labor, and 80% of them were delivered under epidural anesthesia.
- Group B, comprising 36 newborns delivered by cesarean section in labor, whose 1-minute APGAR score was 7 or higher. These babies were subjected to some labor, and 56% of them were delivered under epidural anesthesia.
- Group C, comprising 17 newborns delivered vaginally whose 1-minute APGAR score was 7 or higher. These babies were subjected to the full effect of labor, and only one of them was delivered under epidural anesthesia.
- Group D, comprising the 15 newborns with a 1-minute APGAR score below 7. These were delivered by cesarean section in labor, 53% of them under epidural anesthesia.

The effect of the method of delivery on the acid-base changes in the maternal and the umbilical vessels was studied. Also, the maternal artery, umbilical vein and umbilical artery were compared to one another with respect to base deficit and lactate levels in each of the four groups. Statistical analysis was done using the F-test (analysis of variance) and the t-test, and statistical significance was defined at the 0.05 level.

3 Results

Tab. I outlines the mean maternal and umbilical blood gases and lactate levels with each method of delivery in vigorous newborns. The maternal pH was not affected significantly by the method of delivery. The maternal pCO_2 was highest with elective cesarean section and lowest with vaginal delivery ($p < 0.02$). The maternal base deficit and lactate were lowest with elective cesarean section and highest at the time of vaginal delivery ($p < 0.001$ and $p < 0.005$, respectively). The cord pH was highest with elective cesarean section and lowest with vaginal delivery in both umbilical vein and umbilical artery ($p < 0.001$). The pCO_2 in either umbilical vessel was not significantly affected by the method of delivery. Cord base deficit and lactate levels were lowest with elective cesarean section and highest at the time of vaginal delivery in both umbilical vessels ($p < 0.001$), implying an increase in the concentrations of fixed acids and lactic acid during labor and delivery. The

Tab. I. Maternal and umbilical blood gases and lactate (mean ± SD) in vigorous newborns (1-minute APGAR score ≥ 7)

Parameter	Elective cesarean section (n = 64)	Cesarean section in labor (n = 36)	Vaginal delivery (n = 17)	p value (F-test)
pH				
Maternal artery	7.41 ± 0.06	7.40 ± 0.04	7.38 ± 0.06	NS
Umbilical vein	7.33 ± 0.06	7.31 ± 0.06	7.27 ± 0.08	$p < 0.001$
Umbilical artery	7.28 ± 0.06	7.26 ± 0.06	7.20 ± 0.07	$p < 0.001$
pCO_2 (mm Hg)				
Maternal artery	28.4 ± 5.6	26.8 ± 4.1	24.0 ± 5.4	$p < 0.02$
Umbilical vein	39.0 ± 6.9	39.3 ± 6.7	37.4 ± 5.6	NS
Umbilical artery	48.0 ± 8.6	46.0 ± 9.5	51.0 ± 9.9	NS
Base deficit (mEq/L)				
Maternal artery	5.4 ± 2.6	6.6 ± 2.6	9.3 ± 2.4	$p < 0.001$
Umbilical vein	4.9 ± 2.9	6.3 ± 3.0	8.9 ± 4.1	$p < 0.001$
Umbilical artery	4.0 ± 3.6	6.2 ± 3.5	7.9 ± 3.5	$p < 0.001$
Lactate (mM/L)				
Maternal artery	1.66 ± 0.56	1.65 ± 0.53	2.39 ± 1.37	$p < 0.005$
Umbilical vein	1.91 ± 0.74	2.17 ± 0.73	3.10 ± 1.40	$p < 0.001$
Umbilical artery	2.02 ± 0.91	2.47 ± 0.94	3.42 ± 1.36	$p < 0.001$

Tab. II. Difference in lactate levels between fetus and mother (mean ± SD, mM/L) in vigorous newborns. (1-minute APGAR score ⩾ 7).

Parameter	Elective cesarean section (n = 64)	Cesarean section in labor (n = 36)	Vaginal delivery (n = 17)	p value (F-test)
Difference between umbilical vein and maternal artery	+ 0.24 ± 0.73*	+ 0.52 ± 0.66+	+ 0.66 ± 1.04*	NS
Difference between umbilical artery and maternal artery	+ 0.35 ± 0.91*	+ 0.81 ± 0.81+	+ 0.98 ± 1.35*	$p < 0.02$

* $p < 0.01$ that the mean is higher than zero.
+ $p < 0.001$ that the mean is higher than zero.

lactate levels were also higher in the umbilical artery than in the umbilical vein in all three groups.

The mean lactate differences between fetus and mother in vigorous newborns are detailed in Tab. II. They were significantly positive in all three groups (fetal levels significantly higher than maternal levels). The mean lactate difference between umbilical artery and maternal artery was lowest with elective cesarean section and highest at the time of vaginal delivery ($p < 0.02$). The same trend was observed for the lactate difference between umbilical vein and maternal artery, although it did not achieve statistical significance.

As the depressed newborns were delivered by cesarean section in labor, they were compared to the vigorous newborns delivered by cesarean section in labor (Tab. III). Depressed babies had significantly higher base deficit and lactate levels than vigorous babies in either umbilical vessel. They also had fetal-maternal differences of lactate that were significantly higher than zero ($p < 0.01$) and also significantly higher than the fetal-maternal differences of lactate in vigorous newborns ($p < 0.01$, Tab. III).

The lactate levels were highest in the umbilical artery and lowest in the maternal artery in all four groups (Tabs. I and III). In contrast, the base deficit values were highest in the maternal artery and lowest in the umbilical artery in all three groups of vigorous newborns (Tabs. I and III). It was only in depressed newborns that fetal base

Tab. III. Maternal and umbilical base deficit and lactate (mean ± SD) in vigorous (1-minute APGAR score ⩾ 7) and in depressed newborns (1-minute APGAR score < 7) delivery by cesarean section in labor.

Parameter	Vigorous newborns (n = 36)	Depressed newborns (n = 15)	p value (t-test)
Base deficit (mEq/L)			
Maternal artery	6.6 ± 2.6	7.6 ± 2.8	NS
Umbilical vein	6.3 ± 3.0	9.6 ± 4.5	$p < 0.01$
Umbilical artery	6.2 ± 3.5	9.3 ± 5.6	$p < 0.025$
Lactate (mM/L)			
Maternal artery	1.65 ± 0.53	2.00 ± 0.61	NS
Umbilical vein	2.17 ± 0.73	3.87 ± 2.24	$p < 0.001$
Umbilical artery	2.47 ± 0.94	4.32 ± 3.40	$p < 0.01$
Difference between umbilical vein and maternal artery	+ 0.52 ± 0.66+	+ 1.92 ± 2.04*	$p < 0.001$
Difference between umbilical artery and maternal artery	+ 0.81 ± 0.81+	+ 2.37 ± 3.20*	$p < 0.01$

* $p < 0.01$ that the mean is higher than zero.
+ $p < 0.001$ that the mean is higher than zero.

deficit values were higher than maternal values (Tab. III); even then, the base deficit was higher in the umbilical vein than in the umbilical artery.

4 Discussion

In the present study, we have examined the blood levels of lactate and base deficit in mother and fetus at the time of delivery to study the feto-placental handling of lactate and fixed acids, and to assess the role of lactate as an indicator of neonatal depression.

Of interest is the discrepancy between the direction of the lactate differences and the direction of the base deficit differences. In vigorous babies, the lactate levels decrease from umbilical artery to umbilical vein to maternal artery, whereas the base deficits increase from umbilical artery to umbilical vein to maternal artery. This discrepancy is likely due to the fact that the base deficit values are not measured directly; they are calculated by the blood gas machine on the basis of a nomogram that is based on adult blood [13], and thus may not accurately reflect the concentration of fixed acids in fetal blood. This casts doubt on the use of base deficit comparisons between the maternal and fetal compartments for the study of the exchange of fixed acids across the placenta, and makes lactate a potentially better candidate for evaluation of fetal acidosis. Alternatively, despite the indirect measurement of fixed acids implicit in the base deficit, it suggests that the maternal compartment may have predominantly nonlactate sources of metabolic acidosis compared with the fetus.

Lactate alone may be used rather than the lactate/pyruvate ratio or excess lactate [5] because neither the lactate/pyruvate ratio nor excess lactate appear to be better indices of prenatal oxygen deprivation than the blood concentration of lactate alone [2, 12].

Our results indicate that the blood lactate levels in both mother and the normal fetus increase with labor and reach their highest values at the time of vaginal delivery. The lactate levels are highest in the umbilical artery and lowest in the maternal artery before the onset of labor. The fetal-maternal differences of lactate increase with labor, reaching their highest values at the time of vaginal delivery. This implies increasing fetoplacental production of lactate with increasing duration of labor. These findings are in general agreement with previous studies in the human [2, 4, 7, 9]. A simple passive diffusion mechanism for fetal-maternal transfer of lactic acid has been suggested [9], the net direction of which is usually from fetus to mother, but may be reversed with high levels of maternal lactic acid [2]. HABEREY et al. [4], on the other hand, have proposed a mechanism whereby lactate transfer across the human placenta is facilitated by linking with a hydrogen ion in such a way that net lactate movement occurs from the more acidic side to the less acidic side of the placenta, with the placenta using up about half of the transported lactate. SCHNEIDER et al. [11], however, conducting in vitro perfusion studies on the human placenta, have reported that the well-oxygenated human placenta is a net producer of lactate. Only about 20% of the glucose taken up by the placenta is metabolized aerobically while the rest goes to lactate. About 90% of this lactate is discharged into the maternal circulation while only 10% is transferred to the fetal circulation. The authors suggest that this high rate of lactate production, also seen in tumor tissue, is characteristic of tissues which show rapid cell proliferation without necessarily being an expression of hypoxia. In the presence of fetal hypoxia, we found a substantial rise in umbilical lactate levels and in the fetal-maternal differences of lactate, as seen in the depressed newborns. This has also been reported to occur with the drop in uterine blood flow that accompanies maternal hypotension [1].

The relative placental contribution to this increased lactate production by the fetoplacental unit in response to hypoxia cannot be estimated precisely from the available data. Nevertheless, the significant difference between umbilical venous lactate and maternal blood lactate in vigorous as well as depressed neonates, shows a substantial placental production of lactate (Tab. III). However, since the major part of the placental production of lactate seems to be discharged into the maternal circulation, and since maternal-fetal exchange of lactate across the

placenta is directed mostly from fetus to mother, it is reasonable to assume that the major source of lactate in the fetal circulation is the fetus itself. This should make lactate measurement in fetal scalp blood a useful method for evaluating fetal stress during labor. Whether this is superior to the measurement of scalp blood pH and gases alone is currently being investigated.

Summary

This study attempts to determine the major source of lactate in the normal and in the depressed human fetus, in order to assess the applicability of fetal blood lactate measurement for the evaluation of fetal stress during labor. We obtained umbilical arterial and venous blood samples at delivery in 132 liveborn infants, together with simultaneous maternal radial arterial samples. All samples were analyzed immediately for pH, blood gases, and lactate. In vigorous newborns (1-minute APGAR score $\geqslant 7$), umbilical arterial and venous lactate levels were lowest with elective cesarean section done before the onset of labor, higher with cesarean section performed during labor, and highest at the time of vaginal delivery ($p < 0.001$, Tab. I). Fetal lactate levels were also significantly higher than maternal levels in vigorous newborns ($p < 0.01$), the lactate difference between umbilical artery and maternal artery being lowest with elective cesarean section, higher with cesarean section performed during labor, and highest with vaginal delivery ($p < 0.02$, Tab. II).
Depressed newborns (1-minute APGAR score < 7) had higher umbilical lactates and higher fetal-maternal lactate differences than vigorous newborns ($p < 0.01$, Tab. III).

Our results indicate that the blood lactate levels in both mother and fetus increase with labor and reach their highest values at the time of vaginal delivery. The lactate levels are highest in the umbilical artery, lower in the umbilical vein, and lowest in the maternal artery before the onset of labor. In normal babies, the fetal-maternal differences of lactate increase with labor, reaching their highest values at the time of vaginal delivery. This implies increasing production of lactate with increasing duration of labor. With neonatal depression, we found a significant rise in the umbilical lactate levels and in the fetal-maternal differences of lactate. The increase in the fetal-maternal differences of lactate with labor and with depression points to the fetoplacental unit as the major source of the increased lactate. The relative placental contribution to the increased lactate production in response to hypoxia cannot be estimated from the available data. However, since the major part of the placental production of lactate seems to be discharged into the maternal circulation [11], it is reasonable to assume that the major source of lactate in the fetal circulation is the fetus itself. This should make lactate measurement in fetal scalp blood a useful method for evaluating fetal stress during labor.

Keywords: Fetal lactate level, fetal stress, neonatal depression.

Zusammenfassung

Beziehung zwischen maternalen und fetalen Laktatspiegeln beim Menschen
Ziel dieser Untersuchung war die Bestimmung der Hauptlaktatquelle beim normalen und beim deprimierten menschlichen Feten. Damit sollte überprüft werden, ob die Messung fetaler Laktatspiegel im Blut zur Erfassung eines fetalen Stress unter der Geburt geeignet ist. Bei 132 Lebendgeborenen wurde unmittelbar post partum arterielles und venöses Nabelblut entnommen und simultan die mütterliche Arteria radialis punktiert. In allen Blutproben wurden sofort der pH, die Blutgaswerte und der Laktatspiegel bestimmt. Bei lebensfrischen Neugeborenen (APGAR 1 min p.p. $\geqslant 7$) waren die Laktatspiegel im arteriellen bzw. venösen Nabelblut am niedrigsten nach primärer Sektio vor Wehenbeginn, höher bei Sektio nach Eröffnung der Geburt und am höchsten bei vaginalen Entbindungen ($p < 0{,}001$, Tab. I). Die fetalen Laktatspiegel lagen bei lebensfrischen Neugeborenen signifikant über den mütterlichen Spiegeln ($p < 0{,}01$). Die Unterschiede zwischen Nabelarterienblut und mütterlichem Arterienblut waren bei primärer Sektio am niedrigsten, etwas höher bei Sektio unter der Geburt und am höchsten bei vaginalen Entbindungen ($p < 0{,}02$, Tab. II).

Deprimierte Neugeborene (APGAR 1 min p.p. < 7) wiesen höhere Laktatspiegel im Nabelblut und größere feto-maternale Unterschiede auf als lebensfrische Kinder ($p < 0{,}01$, Tab. III).
Unsere Ergebnisse zeigen, daß sowohl die mütterlichen wie auch die fetalen Laktatspiegel unter der Geburt ansteigen und ihr Maximum zum Zeitpunkt der vaginalen Entbindung erreichen. Vor Wehenbeginn finden sich die höchsten Spiegel in der Nabelarterie, etwas niedrigere in der Nabelvene und die niedrigsten in der mütterlichen Arterie. Die feto-maternalen Unterschiede nehmen bei normalen Feten unter der Geburt zu, wobei die größten Differenzen zum Zeitpunkt der vaginalen Entbindung erreicht werden. Das bedeutet, daß die Laktatproduktion mit der Dauer der Geburt ansteigt. Bei klinisch deprimierten Neugeborenen fanden wir einen signifikanten Anstieg der Laktatspiegel im Nabelblut. Auch die feto-maternale Differenz nahm zu. Dies ist ein Hinweis dafür, daß die feto-plazentare Einheit die Hauptquelle für das angestiegene Laktat darstellt. Der relative Anteil der Plazenta an der erhöhten Laktatproduktion in Folge einer Hypoxie kann jedoch aus den vorliegenden Daten nicht abgeschätzt werden. Wenn aber der größte Teil des durch die Plazenta

produzierten Laktats in den mütterlichen Kreislauf gelangt [11], kann man annehmen, daß im fetalen Kreislauf der Fet selbst die Hauptquelle darstellt. Darum meinen wir, daß die Laktatbestimmung im fetalen Skalpblut eine sinnvolle Methode zur Erfassung eines fetalen Stress unter der Geburt ist.

Schlüsselwörter: Fetaler Laktatspiegel, fetaler Stress, neonatale Depression.

Résumé

Relations entre lactate maternel et lactate fœtal dans l'espèce humaine

Cette étude tente de déterminer la source principale de lactate chez le fœtus humain normal et déprimé, afin d'évaluer l'utilité de la détermination des lactates sanguins fœtaux pour évaluer le stress fœtal au cours du travail. Nous avons obtenu des échantillons de sang ombilical artériel et veineux chez 132 enfants vivants à la naissance, avec simultanément du sang maternel prélevé dans l'artère radiale. Dans tous les échantillons, on a déterminé immédiatement le pH, les gaz sanguins et les lactates. Chez les nouveaux-nés en bon état (APGAR à 1 minute $\geqslant 7$) les taux de lactates dans l'artère et dans la veine ombilicale sont plus bas lorsqu'une césarienne a été effectuée avant le début du travail, plus élevés si la césarienne a été réalisée en cours de travail et encore plus élevés lors d'accouchement par voie basse ($p < 0{,}001$, tab. I). Les taux de lactates fœtaux sont également plus élevés de façon significative chez les enfants en bon état que les taux maternels ($p < 0{,}01$); la différence entre les lactates de l'artère ombilicale et les lactates de l'artère radiale est plus petite avec une césarienne prophylactique, plus élevée lorsque la césarienne a été effectuée en cours de travail et encore plus élevée lors d'accouchements par voie basse ($p < 0{,}02$; tab. II).

Les nouveaux-nés déprimés (score d'APGAR à 1 minute < 7) ont des lactates ombilicaux plus élevés et des différences fœto-maternelles plus élevées que les nouveaux-nés en bon état ($p < 0{,}01$; tab. III).

Nos résultats indiquent que les taux de lactates sanguins et chez la mère et chez le fœtus augmentent au cours du travail et atteignent leurs valeurs les plus élevées au moment de l'accouchement par voie basse. Les taux de lactates sont les plus élevés dans l'artère ombilicale, plus bas dans la veine ombilicale, et les plus bas dans l'artère maternelle avant le début du travail. Chez les enfants normaux, les différences fœto-maternelles de lactates augmentent en cours de travail pour atteindre leurs valeurs les plus élevées au moment de la naissance par voie basse. Cela implique une production accrue de lactates avec l'augmentation de la durée du travail. Lors des dépressions néonatales, nous avons trouvé une élévation significative du taux de lactates ombilicaux, et des différences fœto-maternelles de lactates. L'augmentation des différences fœto-maternelles de lactates avec le travail et avec la dépression met l'accent sur le fait que l'unité fœto-placentaire représente la source principale de l'augmentation des lactates. La contribution placentaire relative à la production accrue de lactates en réponse à l'hypoxie ne peut être estimée à partir des données disponibles. Néanmoins, puisque la majeure partie de la production placentaire de lactates semble être libérée dans la circulation maternelle, il est raisonnable de considérer que la source principale de lactates dans la circulation fœtale est le fœtus lui-même. Ce fait devrait faire de la mesure des lactates dans le sang fœtal prélevé au scalp une méthode utile pour évaluer le stress fœtal au cours du travail.

Mots-clés: Dépression néonatale, stress fœtal, taux de lactates fœtaux.

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